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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,199	05/21/1999	Michael J McCluskie	C1040/7006HC	7506

7590 07/12/2006

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/316,199	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,12,13,15-20,22,25-28,129 and 135-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-9, 12-13, 15-20, 22, 25-28, 129, 135-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 1/30/2006 was entered.

Amended claims 1, 4-9, 12-13, 15-20, 22, 25-28, 129, 135-136 and new claims 137-146 are pending in the present application.

Applicants previously elected the following species in the Amendment filed on 4/3/01: (a) X1X2CGX3X4 wherein X1 is G, X2 is T, X3 is T and X4 is T as a species of CpG motif; (b) macromolecular complexes as a species of a colloidal dispersion system; (c) alum as a species of non-oligonucleotide mucosal adjuvant; (d) a subject at risk of developing an infectious disease as a species of a subject; (e) infectious virus as a species of antigen; and (f) the intranasal route as a species of route of administration.

The examiner noted that the species restriction with respect to cytokine and alum, and between intranasal and oral administration was withdrawn in the Office Action mailed on 6/20/01. Additionally, the species AACpGTT has been rejoined in the examination in the Office action mailed on 2/17/2004; and that the species restriction on a subject was withdrawn in the Office action mailed on 11/2/04. In light of the prior art applied in the Office action mailed on 7/28/05 and below, the species restriction on a colloidal dispersion system and route of administration was also withdrawn.

Accordingly, claims 1, 4-9, 12-13, 15-20, 22, 25-28, 129, 135-136 and new claims 137-146 are examined on the merits herein with the aforementioned elected species and rejoined specific species.

Remarks

In the Amendment filed on 1/30/06, Applicants requested that the Examiner indicated clearly that the Examiner already considered every reference contained in the previously submitted PTO-form 1449s, even though the Examiner has signed, dated and returned them. In response, the Examiner has considered all of them given the time allocated by the Patent Office for the search and examination of a patent application. The examiner further noted that Applicants submitted **285** references for the examiner to consider.

Applicants also requested the examiner to call attorney Maria Trevisan prior to the issuance of a further action. Due to the time constraint and the deadline of this amended case, the examiner did not have the opportunity to contact Ms. Trevisan. However, should Applicants like to have an interview for any reasons after receiving this Office Action, please do not hesitate to contact the examiner to schedule the interview.

Response to Amendment

The rejection under 35 U.S.C. 102(e) as being anticipated by Krieg (US 6,218,371; Cited previously) as evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(e) as being anticipated by Krieg et al. (US 6,239,116; Cited previously) as evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 103(a) as being unpatentable over Morein et al. (U.S. 6,607,732) in view of Krieg et al. (US 6,239,116; Cited previously) was withdrawn in light of Applicant's amendment.

Claim Objections

Claim 9 is objected to because the term "poly[di(carboxylatophenoxy)phosphazene (PCP)" appears to be incomplete, particularly with the absence of a closing square bracket. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

Amended claim 136 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a mucosal immune response having the steps recited in claim 136, in which at least the oligonucleotide and the antigen are both administered intranasally, rectally, intravaginally, ocularly, or by inhalation to the subject;

does not reasonably provide enablement for a method for inducing a mucosal immune response in which the oligonucleotide and the antigen are not administered together to the same site as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for essentially

the same reasons already set forth in the Office action mailed on 7/28/05 (pages 4-8).

This rejection should be applied previously to claim 136.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

When read in light of the specification, the sole purpose for a method of inducing a mucosal immune response in a subject as claimed is to attain prophylactic and/or therapeutic effects. There is no other disclosed use for the induction of a mucosal immune response in a subject. As enablement requires the specification to teach how to make and use the claimed invention, the instant specification is not enabled for the method as claimed for the following reasons.

1. The breadth of the claim

The claim is drawn to a method for inducing a mucosal immune response comprising administering to any mucosal surface of any subject in need of a mucosal immune response an effective amount for inducing a mucosal immune response of an oligonucleotide 8 to 100 nucleotides in length, having a sequence including at least the following formula: 5'-X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3, and X4 are nucleotides, any non-oligonucleotide mucosal adjuvant that is not an immune stimulating complex (ISCOM^{TM}), and any antigen, wherein the antigen is not

encoded in a nucleic acid vector and wherein the oligonucleotide and the non-oligonucleotide mucosal adjuvant are administered intranasally, rectally, intravaginally, ocularly, or by inhalation to the subject, and a cytokine is not administered to the subject. As written, the antigen and the oligonucleotide are not necessarily administered to the same site in the treated subject.

2. The state and the unpredictability of the prior art

At about the effective filing date of the present application (5/22/98), little was known whether a CpG motif containing oligonucleotide is capable of inducing a therapeutic mucosal immune response by itself in a subject against any antigen that the subject is exposed to, particularly the subject is exposed to the antigen at a mucosal surface that is different from that at which the CpG oligonucleotide is administered. Numerous post-filing publications after the effective filing date of the present application still only teach that CpG oligonucleotide is an effective mucosal adjuvant in mice when co-administered with protein antigens as evidenced by the teachings of Moldoveanu et al. (Vaccine 16:1216-1224, 1998; IDS), Davis et al. (J. Immunology 160:870-876, 1998; IDS), McCluskie et al. (J. Immunology 161:4463-4466, 1998; IDS); McCluskie et al. (Current Opinion in Invest. Drugs 2:35-39; 2001; IDS) and McCluskie et al. (Critical Reviews in Immunology 21:103-120, 2001; IDS). With respect to DNA vaccines containing a CpG motif, McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999; Cited previously) have noted that the route of administration and DNA doses as well as numerous other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types

of host immune responses elicited (page 313, see the section titled "Role of CpG immunostimulatory sequences). Additionally, Caufield (WO 98/52962) also already demonstrated the lack of an adjuvant effect in a situation where a CpG containing oligonucleotide was injected in the opposite leg from where the antigen was injected (see example 5 on pages 25-26).

3. The amount of direction or guidance provided

The instant specification fails to provide sufficient guidance for a skilled artisan in the art on how to obtain any therapeutic mucosal immune response against any antigen in any subject, wherein the subject is exposed either passively or actively to the antigen at a different mucosal surface from which the CpG oligonucleotide is administered. There is no evidence in the prior art at the effective filing date of the present application or in the instant disclosure demonstrate that a CpG motif containing oligonucleotide by itself is capable of inducing an effective antigen-specific mucosal immune response that yields prophylactic and/or therapeutic effects in a subject against any antigen that the subject is exposed to. Nor is there any evidence of record indicating or suggesting that a CpG oligonucleotide has an effective adjuvant effect for any antigen that is not co-administered or administered at the same site (including a mucosal surface) as that of the CpG oligonucleotide. As already noted above, Caufield (WO 98/52962) already demonstrated the lack of an adjuvant effect in a situation where a CpG containing oligonucleotide was injected in the opposite leg from where the antigen was injected (see example 5 on pages 25-26). In addition, the instant specification teaches explicitly that CpG alone did not induce IgA in lung washes, however it induced IgA in the feces

but only in some animals (see page 63, lines 20-29), and there is no evidence that the detectable IgA is effective to yield any prophylactic and/or therapeutic effects that are contemplated by Applicants. Even several years after the effective filing date of the present application, McCluskie et al. (Current Opinion in Invest. Drugs 2:35-39; 2001; IDS) still state "[w]e and others have recently shown CpG DNA to be an effective mucosal adjuvant in mice when co-administered with protein antigens" (page 35, col. 2, bottom of second paragraph). It is further noted that the physiological art is recognized as unpredictable (MPEP 2164.03).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the relevant art for the attainment of a therapeutic mucosal immune response against any antigen in any subject, wherein the subject is exposed either passively or actively to the antigen at a different mucosal surface from which the CpG oligonucleotide is administered, and the breadth of the claim, it would have required undue experimentation for one skilled in the art to **make and use** the method as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-9, 12-13, 15-20, 22, 25-28, 129, 135-136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

Claims 1, 136-139, 141 and their dependent claims contain the trademark/trade name (ISCOM™). Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an immune stimulating complex and, accordingly, the identification/description is indefinite. It is noted that claim 9 also contain another trademark/tradename (PROVAX®).

Claim Rejections - 35 USC § 103

Claims 1, 4-9, 12-13, 15-20, 22, 26-28, 129 and 135-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (US 6,239,116; Cited previously) in view of Hutcherson et al. (US 6,727,230 B1; Cited previously) **or** Agrawal et al. (US 6,426,334; Cited previously) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously). ***This is a new ground of rejection.***

Krieg et al discloses a method of stimulating immune activation by administering an isolated immunostimulatory nucleic acid sequence containing a CpG motif represented by the formula: 5'-N1X1CpGX2N2-3', wherein at least one nucleotide

separates consecutive CpGs; X1 is adenine, guanine, or thymine; X2 is cytosine or thymine; N is any nucleotide and N1+N2 is from about 0-26 bases with the proviso that N1 and N2 do not contain a CCGG quadmer or more than one CCG or CGG trimer; and the nucleic acid sequence is from about 8-30 bases in length and wherein the immune activation effects predominantly a Th1 pattern of immune activation (see Summary of the Invention). Krieg et al further teaches that the nucleic acid sequence can be administered to stimulate a subject's response to a vaccine to ameliorate disorders such as cancer, viral, fungal, bacterial or parasitic infection, specifically the nucleic acid sequence can be administered to a subject in conjunction with a particular allergen as a type of desensitization therapy to treat the occurrence of an allergic reaction associated with an asthmatic disorder (col. 6, line 63 continues to line 7 of col. 7). Infectious virus, bacteria, fungi are listed in columns 10-11. The CpG oligonucleotides are stabilized by incorporating a phosphate backbone modification, for example a phosphorothioate or phosphorodithioate modification at the 5' end or 3' end (col. 14, lines 3-32). Krieg et al also specifically teaches the sequence 1826 having the sequence TCCATGACGTTCCTGACGTT is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund's, but without apparent toxicity (col. 22, lines 54-62). Krieg et al. further teaches that the immunostimulatory nucleic acid sequence can be administered to a subject slightly before or at the same time as the vaccine, and that a conventional adjuvant (e.g., aluminum precipitates) may optionally be administered in conjunction with the vaccine, which is minimally comprised of an antigen, as the conventional adjuvant may further

improve the vaccination by enhancing antigen absorption (col. 45, lines 37-46). Routes of administering the immunostimulatory nucleic acid include oral and transdermal and others (col. 46, lines 55-64). It is also noted that a subject having an immune system deficiency such as a subject having a cancer or an infection is a subject in need of at least a mucosal immune response. Krieg et al further discloses that for administration *in vivo*, nucleic acids may be associated with a target cell specific binding agent or be encapsulated in liposomes or virosomes using well known techniques (col. 13, lines 42-47; col. 45, lines 6-17).

Krieg et al. does not disclose specifically the recited routes of administration, even though Krieg et al. teaches that any administration route to a subject can be used, with the preferred routes of administration include oral and transdermal. Krieg et al. also does not teach specifically further administering a boost of the oligonucleotide or a boost of the oligonucleotide and a non-oligonucleotide mucosal adjuvant.

However, at the effective filing date of the present application Hutcheson et al already taught delivering to an infectious subject or a tumor bearing subject an effective amount of a synthetic or ISIS oligonucleotide containing an unmethylated CpG motif by various administration routes including opthalmically, intranasally, rectally, vaginally, orally as well as inhalation to stimulate a cell mediated immune response (see at least Summary of the Invention; col. 7, lines 48-66; Table 1 and Sequence listing). Hutcheson et al. further teaches that dosing is dependent on severity and responsiveness of the condition to be treated, and will normally be one or more doses per day, with course of treatment lasting from several days to several months, and that

an ordinary skilled artisan can easily determine the optimum dosages, dosing methodologies and repetition rates (col. 8, lines 27-34).

Agrawal et al. also taught delivering to an infectious subject or a tumor bearing subject an effective amount of a synthetic oligonucleotide containing an unmethylated CpG motif through various modes of administration that include oral, topical, intranasal, intrarectal among others to stimulate an immune response (col.5, lines 39-43). Agrawal et al. further teaches that administration of the oligonucleotides can be carried out using known procedures at dosages and for periods of time effective to reduce symptoms (col. 5, lines 46-48).

Accordingly, it would have been obvious for an ordinary skilled artisan, particularly an investigator in the art of vaccine, to modify a method of stimulating immune activation of Krieg et al. by also delivering their vaccine composition containing an isolated immunostimulatory nucleic acid sequence at least intranasally, rectally, vaginally, orally as well as inhalation in light of the teachings of either Hutcherson et al. or Agrawal et al. Additionally, it would also have been obvious for an ordinary skilled artisan to administer the composition one or more doses or repetition rates to attain the desired effects in light of the teachings of either Hutcherson et al. or Agrawal et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because these specific routes of delivery have been routinely and successfully used for delivering for a synthetic oligonucleotide containing an unmethylated CpG motif to induce an immune response in an infectious subject or a tumor bearing subject as taught by either Hutcherson et al. or Agrawal et al.

Furthermore, both Hutcherson et al. and Agrawal et al. teach clearly that procedures at dosages and for periods of time effective to attain the desired effects are well known in the art.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Krieg et al., Hutcherson et al. or Agrawal et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art. Particularly, since the modified method that is based on the combined teachings Krieg et al., and either Hutcherson et al. or Agrawal et al. has the same method steps and starting materials as those of the present application, an induction of a mucosal immune response would be expected to occur. Moreover, this is supported by the factual evidence established by McCluskie et al which shows that oligonucleotides containing CpG motifs can induce an antigen-specific mucosal immune response in a subject upon oral, intrarectal or intranasal delivery of an antigen together with the CpG oligonucleotides (see at least Figure 2).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (US 6,239,116; Cited previously) in view of Hutcherson et al. (US 6,727,230 B1; Cited previously) **or** Agrawal et al. (US 6,426,334; Cited previously) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) as applied to claims 1, 4-

9, 12-13, 15-20, 22, 26-28, 129 and 135-146 above, and further in view of Craig (US 6,689,757; Cited previously). ***This is a new ground of rejection.***

The combined teachings of Krieg et al. with either Hutcherson et al. or Agrawal et al. were presented above. However, none of the references teaches specifically a method further comprising administering a B-7 costimulatory molecule.

At the effective filing date of the present application, Craig already taught methods for vaccinating a mammal against a disease using additional factors that include cytokines and/**or** co-stimulatory molecules such as B7-1, B7-2, ICAM-1 and ICAM-3 in conjunction with a nucleic acid and antigen (col. 6, lines 35-49).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method resulting from the combined teachings of Krieg et al. and either Hutcherson et al. or Agrawal et al. by further employing a co-stimulatory molecule such as B7-1, B7-2 in light of the teachings of Craig.

An ordinary skilled artisan would have been motivated to carry out the above modification because the further administration of co-stimulatory molecules such as B7-1 and B7-2 would further enhance the induced immune response in the subject as taught by Craig.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Krieg et al. with either Hucherson et al. or Agrawal et al., along with Craig, and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 136-138 and 142-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briles et al. (U.S. Patent No. 6,042,838) in view of Krieg et al. (U.S. Patent No. 6,194,388; IDS) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously). ***This is a new ground of rejection with respect to the last Office action.***

Briles et al. discloses an immunogenic composition and a method for eliciting an immunological response against pneumococcal surface protein A (PSPA) in a host susceptible to *Streptococcus pneumoniae* by intranasally administering to the host an effective amount of PSPA in the form of a killed whole pneumococci, a lysate of pneumococci or an isolated PSPA or an immunogenic fragment thereof in the presence of an adjuvant, with cholera toxin B as a preferred adjuvant, to protect a host against pneumoccocal colonization and/or systemic infection (see summary of invention, col. 1-7). Briles et al. also teaches that immunostimulatory agents or adjuvants have been used to improve the host immune responses to vaccines, these include intrinsic adjuvants such as lipopolysaccharides which normally are the components of the killed or attenuated bacteria used as vaccines or extrinsic adjuvants such as aluminum hydroxide, LPS, Freund's complete adjuvant and others which are immunomodulators which are typically non-covalently linked to antigens and are formulated to enhance the host immune responses. Briles et al. further discloses that the immunogenic

composition can be prepared as inhalables, sprays and that pump spray or nasal spray or squeeze dispensers (a device) for dispensing a metered dose or a dose with a particular particle or droplet size are commercial available for mucosal administration (col. 3, lines 32-52). Briles et al. further teaches that useful surfactants for the immunogenic composition include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate and others to enhance absorption (col. 6, lines 14-21). Briles et al. further teaches that specific IgA antibodies are induced in secretions of the intestinal, respiratory, and genital tracts, as well as predominantly IgA antibody secreting cells in the intestinal lamina propria and salivary glands. Strong circulatory immune responses are also induced with IgG and IgA antibodies in the serum, and IgG and IgA antibody-secreting cells in the spleen (col. 8, lines 14-34, and examples).

Briles et al. does not teach the use of any oligonucleotide 8 to 100 nucleotides in length, having a sequence including at least the formula: 5'-X1X2CGX3X4-3', wherein C is unmethylated, as an adjuvant in a composition or a method for inducing mucosal immunity to an antigen in a mammalian host via intranasal administration.

However, at the effective filing date of the present application, Krieg et al. discloses various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising the sequence AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teaches that the immunostimulatory oligonucleotides can be used in conjunction with a

vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims).

Accordingly, it would have been obvious for an ordinary skilled artisan, particularly an investigator in the art of vaccine, to modify the immunogenic composition and the method for inducing mucosal immunity against pneumococcal colonization and systemic infection taught by Briles et al. by utilizing at least an immunostimulatory oligonucleotide having the sequence AACGTT taught by Krieg et al. as an adjuvant.

An ordinary skilled artisan would have been motivated to carry out the above modification because Krieg et al. teaches clearly that an immunomodulatory oligonucleotide having a CpG motif can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Briles et al., Krieg et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art. Particularly, since the modified method that is based on the combined teachings Briles et al. and Krieg et al., has the same method steps and starting materials as those of the present application, an induction of a mucosal immune response would be expected to occur. Moreover, this is supported by the factual evidence established by McCluskie et al which shows that oligonucleotides containing CpG motifs can induce an antigen-specific mucosal immune response in a

subject upon oral, intrarectal or intranasal delivery of an antigen together with the CpG oligonucleotides (see at least Figure 2).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

Claims 1, 4-7, 12-13, 18-20, 22, 26, 129, 135, 137-141 and 143-146 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 145 of copending Application No. 10/888,886. ***This is a new ground of rejection.***

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are directed to a method for inducing a mucosal immune response, comprising administering to a subject in need of a mucosal immune response an effective amount for inducing a mucosal immune response of an oligonucleotide 8-100 nucleotides in length, having a sequence including at least the following formula: 5'X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3 and X4 are nucleotides, and an antigen, wherein the antigen is not encoded in a nucleic acid vector, the oligonucleotide and the antigen are both administered vaginally, rectally, intranasally, ocularly, or by inhalation to the subject, a cytokine and an immune stimulating complex (ISCOM^{TM}) are not administered to the subject (claims 137-141 and 143-146); the same method wherein the antigen is not a *Streptococcus pneumoniae* antigen (claim 1 and its dependent claims 4-7, 12-13, 18-20, 22, 26, 129, 135). Claim

145 of the co-pending application 10/888,886 is drawn to a method for inducing IgA secretion in a subject comprising administering to a subject a composition comprising an antigen and a nucleic acid delivery complex having a CpG oligonucleotide associated with a cationic lipid or a sterol in an effective amount for inducing IgA secretion, wherein the antigen is not encoded in a nucleic acid vector, and wherein the composition is administered mucosally in the co-pending Application No. 10/888,886.

The claims of the present application differ from the claim of the copending Application No. 10/888,886 in reciting specific limitation of the imunostimulatory CpG oligonucleotide and the specific delivery routes to the subject for inducing a mucosal immune response; as well as the specific subject and specific antigen in dependent claims. The claims of the present application can not be considered to be patentably distinct over claim 145 of the co-pending Application No. 10/691468 when there are specific preferred embodiments of using an immunostimualtory CpG oligonucleotide having the limitation recited by the claims of the present application (see at least pages 3-9), the same administration routes (page 8, lines 10-11), the same antigen types (page 7, line 24 continues to line 1 of page 8) as well as the same subject to be treated (page 7, lines 19-23) in a method of inducing a mucosal immune response or IgA secretion in a subject. Accordingly, claim 145 of the co-pending application falls within the scope of claims 1, 4-7, 12-13, 18-20, 22, 26, 129, 135, 137-141 and 143-146 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the method being claimed in the co-pending application by utilizing an

immunostimulatory CpG oligonucleotide 8-100 nucleotides in length, having a sequence including at least the following formula: 5'X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3 and X4 are nucleotides, the specific delivery routes, the same subject and antigens that support the instant claims. An ordinary skilled artisan would have been motivated to do this because these preferred embodiments are explicitly disclosed or taught in the co-pending application.

This is a provisional obviousness-type double patenting rejection.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

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